



Clinical trial results:

Phase IIIb, Randomized, Open-Label Study of Pegylated Interferon Alfa-2a in Combination with Lamivudine or Entecavir Compared with Untreated Control Patients in Children with HBeAg-Positive Chronic Hepatitis B in the Immune-Tolerant Phase

Summary

| | |
|--------------------------|-----------------|
| EudraCT number | 2006-000977-31 |
| Trial protocol | GB DE BE IT |
| Global end of trial date | 29 January 2020 |

Results information

| | |
|--------------------------------|----------------|
| Result version number | v1 |
| This version publication date | 01 August 2020 |
| First version publication date | 01 August 2020 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | NV25361 |
|-----------------------|---------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02263079 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | F. Hoffmann-La Roche AG |
| Sponsor organisation address | Grenzacherstrasse 124., Basel, Switzerland, CH-4070 |
| Public contact | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com |
| Scientific contact | F. Hoffmann-La Roche AG, F. Hoffmann-La Roche AG, 41 616878333, global.trial_information@roche.com |

Notes:

Paediatric regulatory details

| | |
|--|-----|
| Is trial part of an agreed paediatric investigation plan (PIP) | No |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | No |

Notes:

Results analysis stage

| | |
|--|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 29 January 2020 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 29 January 2020 |
| Was the trial ended prematurely? | Yes |

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial is to evaluate the efficacy of Pegasys® + lamivudine or entecavir compared with an untreated control in children with CHB, as measured by loss of HBsAg 24 weeks post-end of treatment/end of untreated observation.

Protection of trial subjects:

All study subjects, parent or legal guardian were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 16 June 2014 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Efficacy, Safety |
| Long term follow-up duration | 1 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Australia: 1 |
| Country: Number of subjects enrolled | Belgium: 3 |
| Country: Number of subjects enrolled | Germany: 4 |
| Country: Number of subjects enrolled | United Kingdom: 18 |
| Country: Number of subjects enrolled | Italy: 1 |
| Country: Number of subjects enrolled | Malaysia: 1 |
| Country: Number of subjects enrolled | Russian Federation: 4 |
| Country: Number of subjects enrolled | Turkey: 15 |
| Country: Number of subjects enrolled | Taiwan: 2 |
| Country: Number of subjects enrolled | Ukraine: 1 |
| Country: Number of subjects enrolled | United States: 7 |
| Country: Number of subjects enrolled | Romania: 2 |
| Worldwide total number of subjects | 59 |
| EEA total number of subjects | 28 |

Notes:

Subjects enrolled per age group

| | |
|---|----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 25 |
| Adolescents (12-17 years) | 34 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 22 sites. Enrolment into the study was terminated prematurely. The study included a Pegasys monotherapy arm with 3 enrolled subjects. Due to the low number, data was not analysed and not presented to avoid subject re-identification.

Pre-assignment

Screening details:

The screening period was up to 6 weeks.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|---|
| Are arms mutually exclusive? | Yes |
| Arm title | Peg-IFN-Alfa-2A + Lamivudine or Entecavir |

Arm description:

Subjects received lamivudine or entecavir alone for 8 weeks followed by peg-IFN-alfa-2A in combination with lamivudine or entecavir for 48 weeks.

| | |
|--|-----------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Peginterferon Alfa 2A |
| Investigational medicinal product code | RO025-8310 |
| Other name | Pegasys |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Subjects received Peginterferon Alfa 2A subcutaneously once weekly with dosing based on body surface area (BSA) categories for 48 weeks.

| | |
|--|---------------|
| Investigational medicinal product name | Lamivudine |
| Investigational medicinal product code | |
| Other name | Epivir |
| Pharmaceutical forms | Oral solution |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received 100 mg lamivudine as a film-coated tablet or oral solution once daily at a dose of 3 mg/kg (maximum daily dose 100 mg) or 0.5 mg entecavir as a film-coated tablet or oral solution at a dose of 0.015 mg/kg once daily (maximum dose of 0.5 mg), given alone for 8 weeks then in combination with Pegasys® for 48 weeks.

| | |
|--|---------------|
| Investigational medicinal product name | Entecavir |
| Investigational medicinal product code | |
| Other name | Baraclude |
| Pharmaceutical forms | Oral solution |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received 100 mg lamivudine as a film-coated tablet or oral solution once daily at a dose of 3 mg/kg (maximum daily dose 100 mg) or 0.5 mg entecavir as a film-coated tablet or oral solution at a dose of 0.015 mg/kg once daily (maximum dose of 0.5 mg), given alone for 8 weeks then in combination with Pegasys® for 48 weeks.

| | |
|--|--------------------|
| Investigational medicinal product name | Entecavir |
| Investigational medicinal product code | |
| Other name | Baraclude |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received 100 mg lamivudine as a film-coated tablet or oral solution once daily at a dose of 3 mg/kg (maximum daily dose 100 mg) or 0.5 mg entecavir as a film-coated tablet or oral solution at a dose of 0.015 mg/kg once daily (maximum dose of 0.5 mg), given alone for 8 weeks then in combination with Pegasys® for 48 weeks.

| | |
|--|--------------------|
| Investigational medicinal product name | Lamivudine |
| Investigational medicinal product code | |
| Other name | Epivir |
| Pharmaceutical forms | Film-coated tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Subjects received 100 mg lamivudine as a film-coated tablet or oral solution once daily at a dose of 3 mg/kg (maximum daily dose 100 mg) or 0.5 mg entecavir as a film-coated tablet or oral solution at a dose of 0.015 mg/kg once daily (maximum dose of 0.5 mg), given alone for 8 weeks then in combination with Pegasys® for 48 weeks.

| | |
|------------------|----------------------------|
| Arm title | Untreated Control Subjects |
|------------------|----------------------------|

Arm description:

Untreated control subjects were observed up to 80 weeks.

| | |
|---|-----------------|
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |

| Number of subjects in period 1 | Peg-IFN-Alfa-2A + Lamivudine or Entecavir | Untreated Control Subjects |
|--------------------------------|---|-------------------------------|
| | | |
| Started | 26 | 33 |
| Completed | 23 | 25 |
| Not completed | 3 | 8 |
| Physician decision | 1 | - |
| Consent withdrawn by subject | 2 | 8 |

Baseline characteristics

Reporting groups

| | |
|---|---|
| Reporting group title | Peg-IFN-Alfa-2A + Lamivudine or Entecavir |
| Reporting group description: Subjects received lamivudine or entecavir alone for 8 weeks followed by peg-IFN-alfa-2A in combination with lamivudine or entecavir for 48 weeks. | |
| Reporting group title | Untreated Control Subjects |
| Reporting group description: Untreated control subjects were observed up to 80 weeks. | |

| Reporting group values | Peg-IFN-Alfa-2A + Lamivudine or Entecavir | Untreated Control Subjects | Total |
|--|---|----------------------------|-------|
| Number of subjects | 26 | 33 | 59 |
| Age categorical Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 8 | 17 | 25 |
| Adolescents (12-17 years) | 18 | 16 | 34 |
| Adults (18-64 years) | 0 | 0 | 0 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age Continuous Units: Years | | | |
| arithmetic mean | 11.9 | 10.9 | |
| standard deviation | ± 3.2 | ± 3.7 | - |
| Sex: Female, Male Units: | | | |
| Female | 16 | 14 | 30 |
| Male | 10 | 19 | 29 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| Hispanic or Latino | 1 | 0 | 1 |
| Not Hispanic or Latino | 25 | 33 | 58 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| Asian | 11 | 11 | 22 |
| Black or African American | 4 | 2 | 6 |
| Multiple | 2 | 0 | 2 |
| Other | 0 | 3 | 3 |
| White | 9 | 17 | 26 |

End points

End points reporting groups

| | |
|---|---|
| Reporting group title | Peg-IFN-Alfa-2A + Lamivudine or Entecavir |
| Reporting group description: Subjects received lamivudine or entecavir alone for 8 weeks followed by peg-IFN-alfa-2A in combination with lamivudine or entecavir for 48 weeks. | |
| Reporting group title | Untreated Control Subjects |
| Reporting group description: Untreated control subjects were observed up to 80 weeks. | |
| Subject analysis set title | Intent-to-Treat |
| Subject analysis set type | Intention-to-treat |
| Subject analysis set description: Intent to treat (ITT) population was defined as all subjects who received at least one dose of study medication of treated group. For untreated group, the ITT population included all randomized subjects. | |
| Subject analysis set title | Safety Population |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: The safety population was defined as all subjects who received at least one dose of study medication and had at least one post-baseline safety assessment. For untreated group, the safety population included all randomized subjects who had at least one post-baseline safety assessment. | |

Primary: Proportion of Subjects With Loss of Hepatitis B Surface Antigen (HBsAg) at 24 Weeks Post-End of Treatment/End of Untreated Observation

| | |
|---|---|
| End point title | Proportion of Subjects With Loss of Hepatitis B Surface Antigen (HBsAg) at 24 Weeks Post-End of Treatment/End of Untreated Observation ^[1] |
| End point description: This endpoint is defined as loss of HBsAg at 24 weeks post-treatment (follow-up Week 24)/end of untreated observation (Week 80). The percentage of responders (response rate) and 95% CI (using the Clopper-Pearson method) for the response rate are presented for each group. The analysis population was the Intent-to-Treat (ITT) population, that included all randomized subjects, who received at least one dose of study medication of treated group. For untreated group, the ITT population included all randomized subjects. | |
| End point type | Primary |
| End point timeframe: 24 weeks post-treatment/at the end of untreated observation (Week 80) | |
| Notes: [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point. Justification: Only descriptive statistics was planned to be reported in the endpoint. | |

| End point values | Peg-IFN-Alfa-2A + Lamivudine or Entecavir | Untreated Control Subjects | | |
|----------------------------------|---|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 26 | 33 | | |
| Units: Percentage of Subjects | | | | |
| number (confidence interval 95%) | 3.8 (0.10 to 19.64) | 0.0 (0.00 to 10.58) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects With Loss of HBsAg

| | |
|-----------------|--|
| End point title | Proportion of Subjects With Loss of HBsAg ^[2] |
|-----------------|--|

End point description:

This endpoint is defined as loss of HBsAg at 1 year post-treatment in the treated group. The 95% Confidence Interval of response rate is calculated by Clopper-Pearson method. The analysis population included subjects from the Peg-INF-Alfa-2A arm, who received at least one dose of study medication of treated group. None of the subjects from the untreated group were assessed for this end point at 1 year post-end of treatment as they were only observed up to 80 weeks (=24 weeks post-treatment for treated subjects).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

1 year post-end of treatment (End of treatment = Week 56)

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Data for this endpoint was provided only for those arms which were planned to be reported.

| End point values | Peg-IFN-Alfa-2A + Lamivudine or Entecavir | | | |
|----------------------------------|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 26 | | | |
| Units: Percentage of Subjects | | | | |
| number (confidence interval 95%) | 3.8 (0.10 to 19.64) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects With Loss of Hepatitis B Virus Envelope Antigen (HBeAg)

| | |
|-----------------|--|
| End point title | Proportion of Subjects With Loss of Hepatitis B Virus Envelope Antigen (HBeAg) |
|-----------------|--|

End point description:

This endpoint is defined as loss of HBeAg at 24 weeks post-treatment (follow-up Week 24)/end of untreated observation (Week 80) and at 1 year post-end of treatment in the treated group. The 95% Confidence Interval of response rate is calculated by Clopper-Pearson method. The analysis population was the Intent-to-Treat (ITT) population, that included all randomized subjects, who received at least one dose of study medication of treated group. For untreated group, the ITT population included all randomized subjects. None of the subjects from the untreated group were assessed at 1 year post-end of treatment as they were only observed up to 80 weeks (=24 weeks post-treatment for treated subjects). 9999=not observed

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

24 weeks post-treatment /end of untreated observation (Week 80), and 1 year post-end of treatment (End of treatment = Week 56)

| End point values | Peg-IFN-Alfa-2A + Lamivudine or Entecavir | Untreated Control Subjects | | |
|----------------------------------|---|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 26 | 33 | | |
| Units: Percentage of Subjects | | | | |
| number (confidence interval 95%) | | | | |
| 24 Weeks post-treatment/Week 80 | 3.8 (0.10 to 19.64) | 12.1 (3.40 to 28.20) | | |
| 1 year post-end of treatment | 11.5 (2.45 to 30.15) | 9999 (9999 to 9999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects With Seroconversion to Hepatitis B Surface Antibody (Anti-HBs), Defined as Loss of HBsAg and Presence of anti-HBs

| | |
|-----------------|--|
| End point title | Proportion of Subjects With Seroconversion to Hepatitis B Surface Antibody (Anti-HBs), Defined as Loss of HBsAg and Presence of anti-HBs |
|-----------------|--|

End point description:

This endpoint measures the seroconversion to anti-HBs defined as loss of HBsAg and presence of anti-HBs at 24 weeks post-treatment (follow-up Week 24)/end of untreated observation (Week 80) and at 1 year post-end of treatment in the treated group. The 95% Confidence Interval of response rate is calculated by Clopper-Pearson method. The analysis population was the Intent-to-Treat (ITT) population, that included all randomized subjects, who received at least one dose of study medication of treated group. For untreated group, the ITT population included all randomized subjects. None of the subjects from the untreated group were assessed at 1 year post-end of treatment as they were only observed up to 80 weeks (=24 weeks post-treatment for treated subjects). 9999=not observed

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

24 weeks post-treatment /end of untreated observation (Week 80), and 1 year post-end of treatment (End of treatment = Week 56)

| End point values | Peg-IFN-Alfa-2A + Lamivudine or Entecavir | Untreated Control Subjects | | |
|----------------------------------|---|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 26 | 33 | | |
| Units: Percentage of Subjects | | | | |
| number (confidence interval 95%) | | | | |
| 24 Weeks post-treatment/Week 80 | 3.8 (0.10 to 19.64) | 0.0 (0.00 to 10.58) | | |
| 1 year post-end of treatment | 3.8 (0.10 to 19.64) | 9999 (9999 to 9999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects With Seroconversion to Hepatitis B Envelope Antibody (Anti-HBe), Defined as Loss of HBeAg and Presence of anti-HBe

| | |
|-----------------|---|
| End point title | Proportion of Subjects With Seroconversion to Hepatitis B Envelope Antibody (Anti-HBe), Defined as Loss of HBeAg and Presence of anti-HBe |
|-----------------|---|

End point description:

This endpoint measures the seroconversion to anti-HBe defined as loss of HBeAg and presence of anti-HBe at 24 weeks post-treatment (follow-up Week 24)/end of untreated observation (Week 80) and at 1 year post-end of treatment in the treated group. The 95% Confidence Interval of response rate is calculated by Clopper-Pearson method. The analysis population was the Intent-to-Treat (ITT) population, that included all randomized subjects, who received at least one dose of study medication of treated group. For untreated group, the ITT population included all randomized subjects. None of the subjects from the untreated group were assessed at 1 year post-end of treatment as they were only observed up to 80 weeks (=24 weeks post-treatment for treated subjects). 9999=not observed

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

24 weeks post-treatment /end of untreated observation (Week 80), and 1 year post-end of treatment (End of treatment = Week 56)

| End point values | Peg-IFN-Alpha-2A + Lamivudine or Entecavir | Untreated Control Subjects | | |
|----------------------------------|--|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 26 | 33 | | |
| Units: Percentage of Subjects | | | | |
| number (confidence interval 95%) | | | | |
| 24 Weeks post-treatment/Week 80 | 0.0 (0.00 to 13.23) | 9.1 (1.92 to 24.33) | | |
| 1 year post-end of treatment | 7.7 (0.95 to 25.13) | 9999 (9999 to 9999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects With Different Hepatitis B Virus (HBV) Deoxyribonucleic Acid (DNA) Levels (Less Than [$<$] 20,000 International Units per Milliliter [IU/mL], $<$ 2000 IU/mL, or Undetectable HBV DNA)

| | |
|-----------------|--|
| End point title | Proportion of Subjects With Different Hepatitis B Virus (HBV) Deoxyribonucleic Acid (DNA) Levels (Less Than [$<$] 20,000 |
|-----------------|--|

End point description:

This endpoint measures different HBV DNA levels (<20000 IU/mL, <2000 IU/mL and undetectable) measured by PCR or hybridization at 24 weeks post-treatment (follow-up Week 24)/end of untreated observation (Week 80) and at 1 year post-end of treatment in the treated group. HBV-DNA undetectable is defined as <29 IU/mL. The 95% Confidence Interval of response rate is calculated by Clopper-Pearson method. The analysis population was the Intent-to-Treat (ITT) population, that included all randomized subjects, who received at least one dose of study medication of treated group. For untreated group, the ITT population included all randomized subjects. None of the subjects from the untreated group were assessed at 1 year post-end of treatment as they were only observed up to 80 weeks (=24 weeks post-treatment for treated subjects). 9999=not observed

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

24 weeks post-treatment /end of untreated observation (Week 80), and 1 year post-end of treatment (End of treatment = Week 56)

| End point values | Peg-IFN-Alfa-2A + Lamivudine or Entecavir | Untreated Control Subjects | | |
|---|---|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 26 | 33 | | |
| Units: Percentage of Subjects | | | | |
| number (confidence interval 95%) | | | | |
| HBV-DNA <20000 IU/mL at follow up Week 24/Week 80 | 7.7 (0.95 to 25.13) | 12.1 (3.40 to 28.20) | | |
| HBV-DNA <2000 IU/mL at follow up Week 24/Week 80 | 7.7 (0.95 to 25.13) | 12.1 (3.40 to 28.20) | | |
| HBV-DNA Undetectable at follow up Week 24/Week 80 | 0.0 (0.00 to 13.23) | 6.1 (0.74 to 20.23) | | |
| HBV-DNA <20000 IU/mL 1 year post-end of treatment | 15.4 (4.36 to 34.87) | 9999 (9999 to 9999) | | |
| HBV-DNA <2000 IU/mL 1 year post-end of treatment | 7.7 (0.95 to 25.13) | 9999 (9999 to 9999) | | |
| HBV-DNA Undetectable 1 year post-end of treatment | 0.0 (0.00 to 13.23) | 9999 (9999 to 9999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in HBV DNA Levels in the Peg-INF-Alfa-2A (Treated) Arm

| | |
|-----------------|--|
| End point title | Change From Baseline in HBV DNA Levels in the Peg-INF-Alfa-2A (Treated) Arm ^[3] |
|-----------------|--|

End point description:

This end point presents HBV DNA levels measured at defined time points from Baseline in the Treated arm. The analysis population included subjects from the Peg-INF-Alfa-2A arm, who received at least one dose of study medication of treated group. Only subjects for whom data were collected are included in the analysis.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 8, 20, 32, 44, 56, Follow up Week 4 and 24

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Data for this endpoint was provided only for those arms which were planned to be reported.

| End point values | Peg-IFN-Alpha-2A + Lamivudine or Entecavir | | | |
|--------------------------------------|--|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 26 | | | |
| Units: log ₁₀ IU/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Baseline | 8.02 (± 0.93) | | | |
| Week 8 | 4.74 (± 1.01) | | | |
| Week 20 | 3.54 (± 0.81) | | | |
| Week 32 | 2.56 (± 0.84) | | | |
| Week 44 | 2.15 (± 0.70) | | | |
| Week 56 | 2.21 (± 0.90) | | | |
| Fu Week 4 | 4.34 (± 2.65) | | | |
| Fu Week 24 | 7.31 (± 1.99) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in HBV DNA Levels in the Untreated Control Subjects

| | |
|-----------------|---|
| End point title | Change From Baseline in HBV DNA Levels in the Untreated Control Subjects ^[4] |
|-----------------|---|

End point description:

This end point presents HBV DNA levels measured at defined time points from Baseline in the Untreated Control arm. The analysis population included subjects from the Untreated Control arm. Only subjects for whom data were collected are included in the analysis.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline, Week 32, 56 and End of Untreated Observation (Week 80)

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Data for this endpoint was provided only for those arms which were planned to be reported.

| End point values | Untreated Control Subjects | | | |
|--------------------------------------|----------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 33 | | | |
| Units: log ₁₀ IU/mL | | | | |
| arithmetic mean (standard deviation) | | | | |

| | | | | |
|----------|--------------------|--|--|--|
| Baseline | 8.22 (\pm 1.07) | | | |
| Week 32 | 8.29 (\pm 0.97) | | | |
| Week 56 | 7.57 (\pm 1.96) | | | |
| Week 80 | 7.24 (\pm 2.58) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects With Combined Response for HBeAg Seroconversion (Defined as Loss of HBeAg and Presence of anti-HBe) and HBV DNA Levels <20,000 IU/mL

| | |
|-----------------|---|
| End point title | Proportion of Subjects With Combined Response for HBeAg Seroconversion (Defined as Loss of HBeAg and Presence of anti-HBe) and HBV DNA Levels <20,000 IU/mL |
|-----------------|---|

End point description:

This endpoint measures the combined response for HBeAg Seroconversion and HBV DNA Levels <20,000 IU/mL at 24 weeks post-treatment (follow-up Week 24)/end of untreated observation (Week 80) and at 1 year post-end of treatment in the treated group. The HBeAg is defined as loss of HBeAg and presence of anti-HBe. The 95% Confidence Interval of response rate is calculated by Clopper-Pearson method. The analysis population was the Intent-to-Treat (ITT) population, that included all randomized subjects, who received at least one dose of study medication of treated group. For untreated group, the ITT population included all randomized subjects. None of the subjects from the untreated group were assessed at 1 year post-end of treatment as they were only observed up to 80 weeks (=24 weeks post-treatment for treated subjects). 9999=not observed

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

24 weeks post-treatment /end of untreated observation (Week 80), and 1 year post-end of treatment (End of treatment = Week 56)

| End point values | Peg-IFN-Alpha-2A + Lamivudine or Entecavir | Untreated Control Subjects | | |
|----------------------------------|--|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 26 | 33 | | |
| Units: Percentage of Subjects | | | | |
| number (confidence interval 95%) | | | | |
| 24 Weeks post-treatment/Week 80 | 0.0 (0.00 to 13.23) | 9.1 (1.92 to 24.33) | | |
| 1 year post-end of treatment | 7.7 (0.95 to 25.13) | 9999 (9999 to 9999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects With Combined Response for HBeAg Seroconversion (Defined as Loss of HBeAg and Presence of anti-HBe) and HBV DNA

Levels <2000 IU/mL

| | |
|-----------------|---|
| End point title | Proportion of Subjects With Combined Response for HBeAg Seroconversion (Defined as Loss of HBeAg and Presence of anti-HBe) and HBV DNA Levels <2000 IU/mL |
|-----------------|---|

End point description:

This endpoint measures the combined response for HBeAg Seroconversion and HBV DNA Levels <2000 IU/mL at 24 weeks post-treatment (follow-up Week 24)/end of untreated observation (Week 80) and at 1 year post-end of treatment in the treated group. The HBeAg is defined as loss of HBeAg and presence of anti-HBe. The 95% Confidence Interval of response rate is calculated by Clopper-Pearson method. The analysis population was the Intent-to-Treat (ITT) population, that included all randomized subjects, who received at least one dose of study medication of treated group. For untreated group, the ITT population included all randomized subjects. None of the subjects from the untreated group were assessed at 1 year post-end of treatment as they were only observed up to 80 weeks (=24 weeks post-treatment for treated subjects). 9999=not observed

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

24 weeks post-treatment /end of untreated observation (Week 80), and 1 year post-end of treatment (End of treatment = Week 56)

| End point values | Peg-IFN-Alfa-2A + Lamivudine or Entecavir | Untreated Control Subjects | | |
|----------------------------------|---|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 26 | 33 | | |
| Units: Percentage of Subjects | | | | |
| number (confidence interval 95%) | | | | |
| 24 Weeks post-treatment/Week 80 | 0.0 (0.00 to 13.23) | 9.1 (1.92 to 24.33) | | |
| 1 year post-end of treatment | 7.7 (0.95 to 25.13) | 9999 (9999 to 9999) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects With Adverse Events

| | |
|-----------------|--|
| End point title | Proportion of Subjects With Adverse Events |
|-----------------|--|

End point description:

An adverse event is any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product. Preexisting conditions which worsen during a study are also considered as adverse events. The safety population included all subjects who received at least one dose of study medication and had at least one post-baseline safety assessment. For untreated group, the safety population included all randomized subjects who had at least one post-baseline safety assessment.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to 24 weeks post-treatment/end of untreated observation (Week 80)

| End point values | Peg-IFN-Alfa-2A + Lamivudine or Entecavir | Untreated Control Subjects | | |
|---|---|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 26 | 33 | | |
| Units: Percentage of Subjects | | | | |
| number (not applicable) | | | | |
| With at least one Non-Serious AE | 92.3 | 45.5 | | |
| With at least one Serious Adverse Event (SAE) | 0.0 | 3.0 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Proportion of Subjects with AEs Leading to Dose Modification or Interruption

| | |
|-----------------|---|
| End point title | Proportion of Subjects with AEs Leading to Dose Modification or Interruption ^[5] |
|-----------------|---|

End point description:

This endpoint measures AEs and lab abnormalities leading to dose interruption or dose modification. Does modification included dose reduced, dose increased or drug interrupted. Adverse events included laboratory abnormalities reported as adverse events. The safety population included all subjects who received at least one dose of study medication and had at least one post-baseline safety assessment in the Peg-INF-Alfa-2A treated arm. This end point only applies to the treated group.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline up to 24 weeks post-end of treatment

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Data for this endpoint was provided only for those arms which were planned to be reported.

| End point values | Peg-IFN-Alfa-2A + Lamivudine or Entecavir | | | |
|-------------------------------|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 26 | | | |
| Units: Percentage of Subjects | | | | |
| number (not applicable) | 23.0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Serum Concentration of Peg-INF-Alfa-2A

| | |
|-----------------|---|
| End point title | Serum Concentration of Peg-INF-Alfa-2A ^[6] |
|-----------------|---|

End point description:

The serum concentration of Peg-INF-Alfa-2A was measured in picogram/milliliter. The analysis population was the Peg-INF-Alfa-2A + Lamivudine or Entecavir arm. The untreated arm did not receive any study medication.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

At Weeks 12, 16, 20, 32, 44, 56

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Data for this endpoint was provided only for those arms which were planned to be reported.

| End point values | Peg-INF-Alfa-2A + Lamivudine or Entecavir | | | |
|--------------------------------------|---|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 14 ^[7] | | | |
| Units: pg/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 12 Predose | 8430 (± 6090) | | | |
| Week 16 Predose | 16300 (± 10100) | | | |
| Week 20 Predose | 13800 (± 8740) | | | |
| Week 32 Predose | 14900 (± 7710) | | | |
| Week 32 24-48h Post-dose | 22700 (± 6070) | | | |
| Week 32 72-96h Post-dose | 23000 (± 4900) | | | |
| Week 32 168h Post-dose | 19300 (± 5880) | | | |
| Week 44 Predose | 21900 (± 14200) | | | |
| Week 56 Predose | 25400 (± 13100) | | | |

Notes:

[7] - Only subjects for whom data were collected are included in the analysis.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From Baseline up to 1 year post-end of treatment in the treated arm; From Baseline to end of untreated observation (Week 80) in the untreated group [up to clinical cut-off date 29 Jan 2020]

Adverse event reporting additional description:

The Adverse Event reporting was carried out in the Safety Analysis Population. The Pegasys monotherapy arm (n=3) had no deaths or SAEs, and AEs are not reported in consideration of subject re-identification.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 22.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---|
| Reporting group title | Peg-IFN-Alfa-2A + Lamivudine or Entecavir |
|-----------------------|---|

Reporting group description:

Subjects received lamivudine or entecavir alone for 8 weeks followed by peg-IFN-alfa-2A in combination with lamivudine or entecavir for 48 weeks.

| | |
|-----------------------|----------------------------|
| Reporting group title | Untreated Control Subjects |
|-----------------------|----------------------------|

Reporting group description:

Untreated control subjects were observed up to 80 weeks.

| Serious adverse events | Peg-IFN-Alfa-2A + Lamivudine or Entecavir | Untreated Control Subjects | |
|---|---|-------------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 1 / 33 (3.03%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Infections and infestations | | | |
| PHARYNGITIS | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 1 / 33 (3.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| DEHYDRATION | | | |
| subjects affected / exposed | 0 / 26 (0.00%) | 1 / 33 (3.03%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| Non-serious adverse events | Peg-IFN-Alfa-2A + Lamivudine or Entecavir | Untreated Control Subjects | |
|--|--|--|--|
| Total subjects affected by non-serious adverse events subjects affected / exposed | 21 / 26 (80.77%) | 10 / 33 (30.30%) | |
| Injury, poisoning and procedural complications CONTUSION subjects affected / exposed occurrences (all) LIMB INJURY subjects affected / exposed occurrences (all) | 2 / 26 (7.69%) 7 | 0 / 33 (0.00%) 0 | |
| Nervous system disorders DIZZINESS subjects affected / exposed occurrences (all) HEADACHE subjects affected / exposed occurrences (all) MIGRAINE subjects affected / exposed occurrences (all) | 3 / 26 (11.54%) 5 14 / 26 (53.85%) 91 2 / 26 (7.69%) 2 | 0 / 33 (0.00%) 0 0 / 33 (0.00%) 0 0 / 33 (0.00%) 0 | |
| General disorders and administration site conditions ASTHENIA subjects affected / exposed occurrences (all) FATIGUE subjects affected / exposed occurrences (all) HYPERTHERMIA subjects affected / exposed occurrences (all) INJECTION SITE BRUISING subjects affected / exposed occurrences (all) PAIN | 2 / 26 (7.69%) 2 5 / 26 (19.23%) 11 2 / 26 (7.69%) 3 2 / 26 (7.69%) 2 | 0 / 33 (0.00%) 0 0 / 33 (0.00%) 0 0 / 33 (0.00%) 0 0 / 33 (0.00%) 0 | |

| | | | |
|---|--|---|--|
| <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>3 / 26 (11.54%)</p> <p>5</p> | <p>0 / 33 (0.00%)</p> <p>0</p> | |
| <p>PYREXIA</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>11 / 26 (42.31%)</p> <p>21</p> | <p>0 / 33 (0.00%)</p> <p>0</p> | |
| <p>Gastrointestinal disorders</p> <p>ABDOMINAL PAIN</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>ABDOMINAL PAIN UPPER</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>NAUSEA</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>VOMITING</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>1 / 26 (3.85%)</p> <p>1</p> <p>3 / 26 (11.54%)</p> <p>3</p> <p>4 / 26 (15.38%)</p> <p>5</p> <p>3 / 26 (11.54%)</p> <p>4</p> | <p>2 / 33 (6.06%)</p> <p>2</p> <p>3 / 33 (9.09%)</p> <p>3</p> <p>1 / 33 (3.03%)</p> <p>1</p> <p>1 / 33 (3.03%)</p> <p>1</p> | |
| <p>Respiratory, thoracic and mediastinal disorders</p> <p>EPISTAXIS</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>3 / 26 (11.54%)</p> <p>8</p> | <p>1 / 33 (3.03%)</p> <p>1</p> | |
| <p>Skin and subcutaneous tissue disorders</p> <p>ACNE</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>ALOPECIA</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> <p>ECZEMA</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>2 / 26 (7.69%)</p> <p>2</p> <p>2 / 26 (7.69%)</p> <p>2</p> <p>2 / 26 (7.69%)</p> <p>2</p> | <p>1 / 33 (3.03%)</p> <p>1</p> <p>0 / 33 (0.00%)</p> <p>0</p> <p>0 / 33 (0.00%)</p> <p>0</p> | |
| <p>Musculoskeletal and connective tissue disorders</p> <p>PAIN IN EXTREMITY</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p> | <p>2 / 26 (7.69%)</p> <p>4</p> | <p>1 / 33 (3.03%)</p> <p>1</p> | |

| | | | |
|--|---|--|--|
| MYALGIA subjects affected / exposed occurrences (all) | 2 / 26 (7.69%) 5 | 0 / 33 (0.00%) 0 | |
| Infections and infestations GASTROENTERITIS subjects affected / exposed occurrences (all) INFLUENZA subjects affected / exposed occurrences (all) NASOPHARYNGITIS subjects affected / exposed occurrences (all) UPPER RESPIRATORY TRACT INFECTION subjects affected / exposed occurrences (all) | 2 / 26 (7.69%) 2 1 / 26 (3.85%) 1 3 / 26 (11.54%) 3 2 / 26 (7.69%) 3 | 0 / 33 (0.00%) 0 2 / 33 (6.06%) 2 1 / 33 (3.03%) 1 1 / 33 (3.03%) 1 | |
| Metabolism and nutrition disorders DECREASED APPETITE subjects affected / exposed occurrences (all) | 2 / 26 (7.69%) 2 | 0 / 33 (0.00%) 0 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|----------------|--|
| 08 May 2013 | Modification of Pegasys dosing categories for alignment across pediatric studies and to conform to the recently approved pediatric dosing regimen for hepatitis C; The hepatitis B virus DNA (HBV-DNA) level required for study inclusion has been corrected; To enhance recruitment and avoid unnecessary exclusion of patient with true chronic hepatitis B (CHB) (positive hepatitis B envelope antibody [HBeAg], positive hepatitis B surface antigen [HBsAg], detectable HBV-DNA), the requirement for negative hepatitis B surface antibody (anti-HBs) and hepatitis B envelope antibody (anti-HBe) has been removed from the inclusion criteria. The diagnostic criteria of CHB does not require measurement of antibodies; The seroconversion stopping rule has been updated to reflect the full seroconversion definition of both HBsAg loss and presence of anti-HBs. |
| 11 July 2013 | The Schedule of Assessments have been updated with respect to lactate and tyrosine-methionine-aspartate-aspartate (YMDD). These were originally only included for the Schedule of Assessments for the Pegasys + Lamivudine treatment arm, but it may be difficult to ensure drawing of baseline bloods only after randomization at site. Therefore, these parameters are identical for all patients (regardless of treatment arm), and the YMDD parameter has been moved to screening instead of baseline; Text has been added to reflect the fact that exploratory analyses may be conducted not only to ascertain the presence of YMDD mutations but others as required. |
| 22 August 2013 | The NV25361 protocol version numbers and EUDRACT number have been amended. This study was originally an investigator-lead single-center study sponsored by King's College Hospital/King's College London (KCH/KCL) and, as such, already had a EUDRACT number assigned (2006-000977-31). The KCH/KCL protocol underwent four amendments, with the final amendment being Version 5 dated 29 April 2010. Plans were then agreed with KCH/KCL for Roche to become the study sponsor and continue the study as a multi-center study. Roche prepared a protocol amendment, which was numbered Version 1 (2 January 2013) and a new (different) EUDRACT number (2012-005356-42) was assigned. Roche then prepared a subsequent amendment, Version 2 (8 May 2013). However, the original EUDRACT number should have been maintained and the protocol version should have followed on from the latest KCH/KCL protocol version number such that the subsequent versions amended by Roche should have been Versions 6 and 7, respectively, rather than Versions 1 and 2. In the future, the protocol version numbers will continue to follow on sequentially from the KCH/KCL protocol version numbering under the original EUDRACT number assigned at the start of the study (2006-000977-31). |

| | |
|------------------|--|
| 03 February 2014 | <p>The Pegasys monotherapy arm has been removed. Concerns regarding the probable low response rates to treatment with Pegasys monotherapy were raised by the study Data Safety Monitoring Board (DSMB) members and potential study investigators during feasibility; Some subjects were recruited into the study under the previous single-site investigator led three-arm study, which included the Pegasys monotherapy arm, and have all now completed their treatment. Text has been included to say that these subjects will roll over into the Roche-sponsor protocol and all data will be reported when the study has been completed. The Pegasys monotherapy schedule of assessments has been updated to include the long-term follow-up period for these subjects; The primary endpoint has been changed from seroconversion to anti-HBs at 1-year post-end of treatment/end of untreated observation to loss of HBsAg at 24 weeks post-end of treatment/end of untreated observation; The secondary endpoints and schedule of assessments have been updated accordingly, and the length of the untreated observation period has been reduced from 100 weeks to 80 weeks to coincide with the earlier primary endpoint; The safety objectives of the study have been updated to clarify that assessment of AEs will include neurological and psychiatric events; For clarity, the efficacy and safety outcome measures have been updated to include the timepoints at which they will be measured; For consistency, AEs of concern have been amended to non-serious AEs of special interest; The diagnosis of CHB is defined as presence of HBsAg for 6 or more months. Hence, the inclusion criterion for positive HBsAg and HBeAg has been changed from more than 1 year to more than 6 months prior to baseline to ensure that eligible subjects diagnosed with CHB within 6-12 months are not unnecessarily excluded. The seroconversion stopping rule has been removed.</p> |
| 26 June 2014 | <p>Analysis of anti-drug antibodies (ADAs) has been added as an exploratory objective in order to follow regulatory guidelines for increased level of immunogenicity testing for new indications (EMA 2008 – Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins); The Ministry of Healthcare of the Russian Federation requires completion of efficacy and safety clinical studies with Pegasys in combination with lamivudine in children with Hepatitis B aged 12 to 17 years of age prior to enrollment of children below 12 years of age. Therefore, the age inclusion criterion has been updated, specifically for Russia, to specify that only patients ≥ 12 years old can be enrolled in this study; The inclusion criterion regarding informed consent has been updated to clarify that those subjects <18 years of age at baseline who are legally considered to be adults according to national legislation must consent in their own right if required by national legislation. In addition, the informed consent section has been updated to clarify that minors who attain legal adulthood during the course of the study must consent in their own right at that time, if required by national legislation.</p> |
| 31 July 2015 | <p>Randomization stratification factor (HBV genotype) has been amended from 'genotype A vs non-A' (2 levels) to 'genotype A vs. B/C vs. D/others' (3 levels) to prevent any potential imbalance of HBV genotype allocation between the 2 randomized arms, since it is expected that reasonable proportions of B,C and D HBV genotypes will be recruited. Sub-analyses from the Pegasys adult immune-active CHB study) have shown different efficacy response according to HBV genotype, with response rates being similar in genotypes B and C; Pegasys dose modification guidance has been updated with recommendations for dosage modification for management of psychiatric disorders as outlined in Table 3 of the Pegasys United States Prescribing Information (USPI) dated March 2015; Assessments on sexual maturation (Tanner staging, date of menarche onset) have been added following an FDA request, and relevant section and the schedule of assessments have been updated accordingly; Pharmacokinetic (PK) sampling has been revised.</p> |

| | |
|------------------|---|
| 15 February 2016 | Study treatment has been modified to include entecavir as a nucleoside analogue option for the combination treatment with Pegasys. Prior to randomization investigators will choose between lamivudine or entecavir. Subjects are treated for the 8-week lead-in phase and the subsequent 48-week Pegasys-combination phase with the same nucleoside analogue throughout the study (if applicable); The Ministry of Healthcare of India required the exclusion of younger subjects from this study. Therefore, the age inclusion criterion has been updated, specifically for India, to specify that only subjects ≥ 12 years old can be enrolled in this study; The inclusion criterion regarding HBV DNA level has been updated to $> 20,000$ IU/mL following review of published data and guidelines on the management of hepatitis B of patients with CHB in the immune-tolerant phase as well as following recommendation of Health Authorities that have evaluated this protocol; The primary analysis of the study has been updated to include the new study treatment option, Pegasys + entecavir. Furthermore testing of the primary endpoint has been updated to clarify that it is a superiority test. |
| 26 October 2018 | Results from two multicenter clinical trials (sponsored by the National Institutes of Health [NIH]) evaluating the entecavir plus Pegasys treatment regimen in subjects with immune-tolerant chronic hepatitis B (CHB) were made available in October 2017 at the American Association for the Study of Liver Diseases Congress in Washington, USA. These two NIH studies demonstrated minimal to no efficacy of the intervention in both adult and pediatric subject populations with immune-tolerant CHB. Moreover, both studies had a similar design to Study NV25361. The conclusion was that the combination of entecavir with Pegasys, administered for up to 48 weeks, rarely led to loss of hepatitis B envelope antigen with sustained suppression of hepatitis B virus (HBV) DNA levels and was associated with frequent but not serious adverse events. The authors also concluded that more potent and more broadly targeted regimens against HBV are needed to treat children in the immune-tolerant phase of chronic HBV infection. Because of the similar study design, treatment regimen and efficacy assessments compared with these two NIH-sponsored studies, Study NV25361 was not expected to demonstrate efficacy in the target subject population. Based on the results of the NIH pediatric study and following a Pediatric Investigational Plan (PIP) modification procedure, the PDCO agreed in March 2018 to modify the PIP for Pegasys and remove Study NV25361 from the PIP commitments. |
| 26 October 2018 | After this decision, the Sponsor terminated recruitment in the study on 28 March 2018 after enrollment of 62 patients (26 patients had been randomized to the active combination treatment, and 3 subjects had been randomized to Pegasys monotherapy before Roche became the study sponsor). This decision to terminate recruitment was also in accordance with the recommendation from the Data Safety Monitoring Board on 22 March 2018 based on the NIH results demonstrating minimal efficacy and a changed benefit-risk assessment. No specific safety concerns were identified in their scheduled review of the study. The protocol for Study NV25361 has been amended because of the expected lack of efficacy of the treatment regimen and the premature termination of recruitment. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

The study was terminated in accordance with the recommendation from the Data Safety Monitoring Board (DSMB) to terminate enrolment on the basis of low efficacy and a changed benefit risk assessment.

Notes: